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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
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09/051,034 03/31/98 MCKENZIE

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HM22/1002

EXAMINER

BRUNOVSKIS, F

ART UNIT	PAPER NUMBER
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1632

DATE MAILED:

10/02/01

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary

Application No.	Applicant(s)	
09/051,034	MCKENZIE ET AL.	
Examiner	Art Unit	
Peter Brunovskis	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) Responsive to communication(s) filed on 30 July 2001.

2a) This action is FINAL. 2b) This action is non-final.

3) Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4) Claim(s) 1-15, 17-24 and 26-29 is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5) Claim(s) _____ is/are allowed.

6) Claim(s) 1-15, 17-24 and 26-29 is/are rejected.

7) Claim(s) _____ is/are objected to.

8) Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9) The specification is objected to by the Examiner.

10) The drawing(s) filed on _____ is/are: a) accepted or b) objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) The proposed drawing correction filed on _____ is: a) approved b) disapproved by the Examiner.
If approved, corrected drawings are required in reply to this Office action.

12) The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13) Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) All b) Some * c) None of:

1. Certified copies of the priority documents have been received.

2. Certified copies of the priority documents have been received in Application No. _____.

3. Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14) Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) The translation of the foreign language provisional application has been received.

15) Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) Notice of References Cited (PTO-892)

2) Notice of Draftsperson's Patent Drawing Review (PTO-948)

3) Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____.

4) Interview Summary (PTO-413) Paper No(s) _____.

5) Notice of Informal Patent Application (PTO-152)

6) Other: _____

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DETAILED ACTION

The request filed on 7/30/01 for a Continued Prosecution Application (CPA) under 37 CFR 1.53(d) based on parent Application No. 09/051,034 is acceptable and a CPA has been established. An action on the CPA follows.

Amendment of claims 1-3, 5-15, 17-19, 23, and 24 is acknowledged, as well as cancellation of claims 16 and 25. Any objections or rejections made in a previous Office Action that are not herein reinstated have been withdrawn. Unless otherwise indicated, arguments directed to rejections rendered moot by Applicants amendments or Examiner's withdrawal will not be further addressed or acknowledged. Claims 1-15, 17-24, and 26-29 are pending in the instant application.

Drawings

Pending formal approval from the draftsman, the proposed changes to the drawings filed 4/02/01 appear to obviate the objections set forth in the Office Action of 1/30/01.

Claim Objections

Newly amended claims 11 and 15 have not been entered, because the amendment to the claim is not in accordance with 37 CFR 1.121(a)(2)(ii) which states:

(ii) Claim cancellation or rewriting: A claim may be amended by directions to cancel the claim or by rewriting such claim with underlining below the matter added and brackets around the matter deleted. The rewriting of a

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claim in this form will be construed as directing the deletion of the previous version of that claim. If a previously rewritten claim is again rewritten, underlining and bracketing will be applied relative to the previous version of the claim, with the parenthetical expression "twice amended," "three times amended," etc., following the original claim number. The original claim number followed by that parenthetical expression must be used for the rewritten claim. No interlineations or deletions of any prior amendment may appear in the currently submitted version of the claim. A claim canceled by amendment (not deleted and rewritten) can be reinstated only by a subsequent amendment presenting the claim as a new claim with a new claim number.

Newly amended claim 11 includes the limitation "any one of claims 1 to 10" which was previously deleted and replaced with the insertion --claim 1-- in the preliminary amendment of 3/31/98. Moreover, the limitation "any one of claims 1 to 10" is not underlined. Further, the limitation of a nucleic acid "which encodes the NH₂ terminal cytoplasmic tail of GT attached to the transmembrane, stem and catalytic domains of Ht" in lines 1-3 is not underlined as required, since this limitation was not entered as set forth in the Office Action of 1/30/01.

Newly amended claim 15 does not recite (or denote) the SEQ ID NOs corresponding to their respective peptide sequences in accordance with the amendment of 11/06/00.

For purposes of compact prosecution, newly amended claims 11 and 15, as filed in the amendment of 4/02/01 will be examined on their merits.

Claims 19, 22, and 28 are objected to for the following informalities: Claims 19 and 28 are objected to for their misspelling of "cytoplasmuc" (cl. 19, line 7) and "fucosyltransferase" (cl. 28, line 2), respectively. Claim 22 is objected to for not being amended in accordance with the election of 1/24/00. As stated in the election requirement of 12/23/99, upon election of Group I, claim 22 would be examined to the extend that it reads on *cells* comprising the nucleic acid of

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group I, not organs or transgenic animals. Appropriate correction is required. Amending the claim to --An isolated cells comprising the nucleic acid of claim xx-- would obviate the objection.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-14, 16-25 remain rejected under 35 U.S.C. 112, second paragraph, for the reasons of record set forth in the Office Action of 1/30/01 and for the reasons set forth below as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1, 11, 17-19, 26 (and dependent claims) are indefinite in their recitation of the term "cytoplasmic tail" since it is unclear how this term is defined, what its metes and bounds are or what structural relationship exists between the cytoplasmic tail and "localization signal" and/or the "different glycosyltransferase".

Claim 8 is indefinite in its recitation of the limitation "wherein the localization signal is from a cell that belongs to the same species as the cell of claim 1" since it is unclear how "species" relates contextually to the localization signal and the different recited cells. Amending the claim to recite --wherein the localization signal is from the same cell type as the cell of claim 1-- would obviate the rejection.

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Claim 9 (and dependent claims) is indefinite in its recitation of the phrase "which transferase" since it is not clear what this phrase is directed to, the H transferase, the galactosyltransferase or the chimeric enzyme. Further, it is not clear how the phrase "to thereby cause hyperacute rejection" relates contextually to the product expressed from the nucleic acid of the instant claim, since the claim recites a composition not a method of causing hyperacute rejection.

Claim 11 is indefinite in its recitation of the term "Ht" since it is unclear how this term is defined or what its metes and bounds are.

Claim 11 is indefinite in its recitation of "[t]he nucleic acid according to any one of claims 1 to 10" since it is unclear how this limitation relates to the structural limitations that follow.

Claims 18 and 19 (and dependent claims) recite the limitation "said product" in lines 9 and 11, respectively. There is insufficient antecedent basis for this limitation in the claim. Amending the claims to --said carbohydrate comprises an epitope-- would obviate the rejection.

Claim 23 is indefinite in its recitation of the limitation "having reduced levels of a carbohydrate on its surface" since it is unclear whether this limitation refers to a property of the animal or to a result occurring on account of expressing the expression unit in said animal. Substituting the phrase "which when used to transform a cell..." with the phrase --in a cell resulting in reduced levels of carbohydrate on its surface-- would obviate the rejection.

Claim 24 is indefinite in its recitation of "A retroviral-packaging cassette...according to claim 23" since there is no apparent nexus between a packaging cassette and the expression unit

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of claim 23. Packaging cassettes comprise sequences for making viral particles, not transgenes as exemplified in the base claim (i.e. claim 1). Deletion of “retroviral-packaging cassette” would obviate the rejection.

Claim 26 (and dependent claim 27) is indefinite in its recitation of “carbohydrate modifying enzyme” since it is unclear how this term is defined or what its metes and bounds are. Further, the claim is indefinite in its recitation of the limitation “and a localization signal of a different glycosyltransferase” (and “different glycosyltransferase” (lines 6, 8, 9, and 11) since the claim does not necessarily require a catalytic domain from e.g. a “first glycosyltransferase” *per se*, but can alternatively utilize a catalytic domain from a “carbohydrate modifying enzyme”. Extending the recitation of the localization signal limitation to the carbohydrate modifying enzyme and extending the scope of the “different glycosyltransferase” limitation to alternatively include “different carbohydrate modifying enzyme” as well would obviate the rejection.

Claim 28 is indefinite in its recitation of the term “said nucleic” in line 3 which is incomplete. Amending the claim to --said nucleic acid-- would obviate the problem.

Claim 28 is indefinite in its recitation of the phrase “whereby said nucleic is expressed in a cell wherein said chimeric enzyme is located in a cell compartment or organelle where it is able to compete for substrate with the $\alpha(1,3)$ galactosyltransferase and wherein the $\alpha(1,3)$ galactosyltransferase is located in the same compartment or organelle as said chimeric enzyme, resulting in...” since there is not a clear nexus between *expression* (or competition) in a cell and *location* in a cell compartment or organelle. Further, there is no point of comparison for the

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phrase “resulting in reduced levels of a product”. Amending the claim to --wherein expression of said nucleic [acid] in a cell results in localization of said chimeric enzyme in the same cell compartment or organelle in which α (1,3) galactosyltransferase is naturally present so as to allow competition for substrate between the chimeric enzyme and the galactosyltransferase so as to result in reduced levels of a product from the α (1,3) galactosyltransferase when compared with the level of said product in a cell wherein the chimeric enzyme is not expressed-- would obviate the rejection.

Claims 28 and 29 are indefinite in their recitation of the phrase “wherein said product is an epitope” since it is not clear whether the product is limited to this epitope (e.g. Gal 1 α (1,3)-Gal epitope) or whether the product *comprises* this epitope. Amending the claim to --wherein said product comprises an epitope-- would obviate the problem.

Claim 29 is indefinite in its recitation of the phrase “said localization signal being specific for a trans Golgi” is indefinite because it is unclear what structural relationship exists between the localization signal and the trans Golgi. Further, the phrase “specific for a trans Golgi appears to be incomplete. Amending the claim to --said signal conferring localization to a trans Golgi cell compartment-- would obviate the rejection.

Claim 29 is further indefinite (as in claim 28) since there is not a clear nexus between *expression* (or competition) in a cell and *location* in a cell compartment or organelle and because there is no point of comparison for the phrase “resulting in reduced levels of a product”.

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Amending the claim in accordance with the analogous suggestions directed to claim 28 would obviate the rejection.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-15, 17-24, and 26-29 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. 37 CFR 1.118 (a) states that “No amendment shall introduce new matter into the disclosure of an application after the filing date of the application”.

Claims 1-15, 17-24, and 26-29 recite limitations that are not clearly described in the instant specification. Specifically, there does not appear to be support for methods of compositions comprising limitations directed to “cytoplasmic tail”, the genus of enzymes comprising “carbohydrate modifying enzymes”, or a generic nucleic acid embodiment comprising a localization signal “specific for a trans Golgi”.

MPEP 2163.06 notes “If new matter is added to the claims, the examiner should reject the claims under 35 U.S.C. 112, first paragraph - written description requirement. *In re Rasmussen*,

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650 F.2d 1212, 211 USPQ 323 (CCPA 1981).” MPEP 2163.02 teaches that “Whenever the issue arises, the fundamental factual inquiry is whether a claim defines an invention that is clearly conveyed to those skilled in the art at the time the application was filed...If a claim is amended to include subject matter, limitations, or terminology not present in the application as filed, involving a departure from, addition to, or deletion from the disclosure of the application as filed, the examiner should conclude that the claimed subject matter is not described in that application. MPEP 2163.06 further notes “When an amendment is filed in reply to an objection or rejection based on 35 U.S.C. 112, first paragraph, a study of the entire application is often necessary to determine whether or not “new matter” is involved. *Applicant should therefore specifically point out the support for any amendments made to the disclosure*” (emphasis added).

Claims 1-14 and 17-25 remain rejected and claims 15 and 26-29 are rejected under 35 U.S.C. 112, first paragraph, for the reasons of record set forth in the Office Actions of 3/09/00 and 1/30/01, and for the reasons set forth below, because the specification, while enabled for compositions or methods comprising chimeric enzymes that include functional domains from fucosyltransferases or galactosyltransferases, as exemplified by gtHT or pgHT for targeting localization to the Golgi resulting in reducing levels of Gal 1 α (1,3)-Gal epitope on the surface of cells, does not reasonably provide enablement for the broad scope of recited chimeric enzymes comprising any and all glycosyltransferase functional domains other than those comprising localization domains of α (1,3) galactosyltransferase and/or catalytic domains from

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fucosyltransferases. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The newly amended claim broaden the scope of the claimed embodiments to include catalytic domains from the genus of “carbohydrate modifying enzymes” and to include cytoplasmic tails from different glycosyltransferases, including those for directing chimeric enzymes to the “trans-Golgi”. The specification does not provide sufficient guidance either defining the scope of these embodiments or teaching how to make and use such embodiments commensurate with the scope of the claimed subject matter--particularly as related to reducing epitope levels associated with hyperacute rejection. The specification admits that “work by the inventors focused on chimeric H transferase” and suggests that “other glycosyltransferase enzymes may also be produced in accordance with the invention” (p. 3, lines 25-28). However, there is not sufficient guidance provided for enabling any other nucleic acid embodiments for reducing epitopes associated with hyperacute rejection apart from those in the working examples. In the absence of such specific guidance it would require undue experimentation to make and use the breadth of subject matter covered in the instant claims.

To the extent that the claims broadly embrace other such embodiments, the instant invention, as claimed, falls under the “germ of an idea” concept defined by the CAFC. The court has stated that “patent protection is granted in return for an enabling disclosure, not for vague intimations of general ideas that may or may be workable”. The court continues to say that

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“tossing out the mere germ of an idea does not constitute an enabling disclosure” and that “the specification, not knowledge in the art, that must supply the novel aspects of an invention in order to constitute adequate enablement”. (See *Genentech inc v. Novo Nordisk A/S* 42 USPQ2d 1001, at 1005). The claimed generic compositions and methods constitute such a “germ of an idea”.

Applicant's arguments filed 4/02/01 have been fully considered but they are not persuasive. The response contends that “the claims have been amended to recite that the product is an epitope reactive with antibodies that cause hyperacute rejection” (p. 7) and that the Declaration of Mauro Sergio Sandrin sets forth details of experiments showing that chimeric glycosyltransferases other than those specifically exemplified in the application are able to reduce the gal epitope in accordance with the invention. First, it is noted that Figure 1 of the faxed declaration cannot be evaluated since the figure panels are completely black.

Nevertheless, Applicants declaration and amendment directed to claims that recite an epitope reactive with antibodies causing hyperacute rejection only provide a basis for enabling claims directed to embodiments limited to those comprising functional domains from fucosyltransferases and galactosyltransferases for the expressed purpose of reducing gal epitope levels on the surface of cells, not any and all generic epitopes or any and all glycosyltransferase functional domains. The declaration by Dr. Sandrin is limited to chimeric enzymes comprising catalytic domains or localization domains from *fucosyltransferases*. There is no evidence or indication of specific guidance from the specification for other chimeric enzyme embodiments, including those comprising functional domains from other glycosyltransferases, such as

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sialyltransferase or from “carbohydrate [or non-carbohydrate] modifying enzymes”, such as galactosylsulphating enzymes or phosphorylating enzymes, or any theoretical basis for using other such domains. For example, neither the response, nor the declaration provides a sufficient basis for functional interchangeability between functional domains of other glycosyltransferases, carbohydrate modifying enzymes, such as galactosylsulphating enzymes or phosphorylating enzymes within the context of reducing hyperacute rejection-associated epitopes. Further, the specification does not teach or provide any other examples of carbohydrates or products associated with hyperacute rejection other than those carrying the Gal 1 α (1,3)-Gal epitope. Thus, have failed to overcome the *prima facie* case for lack of enablement as directed to the broad scope of chimeric glycosyltransferase hybrids as claimed.

Based on the problems and lack of uniformity or knowledge concerning localization signals as described in e.g. the Office Actions of 3/9/00 (e.g. p. 11-13) and 1/30/01 (e.g. p. 10-11), the lack of specific guidance for using catalytic domains from non-fucosyltransferase enzymes, and the difficulty in identifying appropriate localization signals and/or catalytic domains for a given glycosyltransferase and/or carbohydrate modifying enzyme, it would require undue experimentation to enable the broad scope of embodiments for reducing generic hyperacute rejection-associated epitope levels commensurate with the scope of the claimed invention. This is particularly the case, since the specification fails to provide adequate guidance or materials for making and using catalytic domains or localization signals from the broad range of mammals recited in e.g. claim 7, particularly since most of them haven’t yet been isolated or described.

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Amending the claims to be limited to compositions comprising functional domains from fucosyltransferases and galactosyltransferases for reducing Gal 1 α (1,3)-Gal epitope levels would obviate this basis for the rejection.

Further, when read in light of the specification, claims 18-19 and 22 recite organs or methods of reducing hyperacute rejection-associated epitopes in cells which are interpreted to embrace methods for xenotransplantation comprising *ex vivo* or *in vivo* use of nucleic acids for gene therapy use in mammals wherein cells or organs comprising such are programmed to be immunologically acceptable as a consequence of downregulation of carbohydrate epitopes recognized as non-self. The specification fails to provide an enabling disclosure for such embodiments, essentially for the reasons previously set forth in the Office Action of 3/9/00 and for the following additional reasons below. Neither the specification, nor Applicants response addresses the problems and unpredictability in the *in vivo* gene delivery art nor does the specification provide adequate guidance teaching one of ordinary skill in the art how to make and use the claimed invention for either direct *in vivo* delivery of glycosyltransferase expression constructs or use of nucleic acids for producing cells for *ex vivo* or *in situ* gene therapy resulting in e.g. cells or tissues “suitable for transplantation.” Amendment of the claimed methods to recite methods of reducing the Gal 1 α (1,3)-Gal epitope in cultured cells would obviate the basis for the rejection as directed to lack of enablement over *in vivo* gene delivery or *ex vivo* cell transplantation.

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It would require undue experimentation for one skilled in the art to make and use the claimed invention. Applicants have failed to present any new or convincing arguments to rebut those set forth in the Office Actions of 3/09/00 or 1/30/01 or the arguments presented herein, and have therefore failed to overcome the *prima facie* case for lack of enablement set forth therein.

Certain papers related to this application may be submitted to Art Unit 1632 by facsimile transmission. The FAX number is (703) 308-4242 or 305-3014. The faxing of such papers must conform with the notices published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 CFR 1.6(d)). NOTE: If applicant *does* submit a paper by FAX, the original copy should be retained by applicant or applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED, so as to avoid the processing of duplicate papers in the Office.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Peter Brunovskis whose telephone number is (703) 305-2471. The examiner can normally be reached on Monday through Friday from 8:30 AM to 5 PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Karen Hauda can be reached at (703) 305-6608.

Any inquiry of a general nature or relating to the status of this application should be directed to the Patent Analyst, Patsy Zimmerman whose telephone number is (703) 308-8338.

Peter Brunovskis, Ph.D.
Patent Examiner
Art Unit 1632

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